REMARKS

Claims 9 and 11-20 are pending. Claims 1-8 have been cancelled as being drawn to a non-elected invention. Claim 10 has been cancelled and the subject matter of claim 10 has been incorporated into claim 9. Claims 9, 12-13, and 18-20 have been amended herein. The amendments are supported by the claims as originally filed and by disclosure at page 5, lines 5-6 of the specification. No new matter is added.

Information Disclosure Statement

Pursuant to Examiner's request, an additional copy of the Information Disclosure Statement and Supplemental Information Disclosure Statement references are attached.

35 U.S.C. § 102(b)

Claims 9, 11, 14, 15, 16, and 20 were rejected for anticipation by O'Leary *et al.* This rejection is traversed.

On pages 2-3 of the OA, the Examiner states:

> O'Leary *et al.* discloses a method of inhibiting cancer cell growth by administering a compound that can be used to inhibit both angiogenesis and DNA topoisomerase activity, therefore also a simultaneous administration, wherein the compound is a camptothecin compound that is capable of performing both desired effects. Furthermore, O'Leary *et al.* also discloses specific camptothecin molecules, including CPT-11, topotecan, and 9-AC[3].

Amended claim 9 requires administration of a thrombospondin compound and a DNA topoisomerase inhibitor. Claim 9 is not anticipated because O'Leary *et al.* do not disclose a method of inhibiting cancer cell growth by administering both a thrombospondin compound and a DNA topoisomerase. Claims 11, 14, 15, 16, and 20 depend from claim 9. Therefore, this rejection should be withdrawn.

35 U.S.C. § 103(a)

Claims 9-20 were rejected for obviousness over O'Leary *et al.* in view of Sheibani *et al.* and Streit *et al.* This rejection is traversed.

As discussed above, O'Leary *et al.* do not teach administration of a thrombospondin compound and a DNA topoisomerase inhibitor. Regarding the combination of O'Leary *et al.* in view of Sheibani *et al.* and Streit *et al.* the Examiner states that O'Leary *et al.* suggest that a combination of camptothecin compounds with endogenous inhibitors of angiogenesis would improve antitumor efficacy. The Examiner states that "[o]ne of skill would be motivated to attempt the combination because the prior art suggests that success could be achieved if a combination of the separate components were added together, thereby leading to a more potent effect." (emphasis added; *see* OA at pages 4-5).

O'Leary *et al.* describe antiangiogenic agents, but fail to disclose or suggest the inhibitors required by the amended claims. Specifically, O'Leary *et al.* state: "Still another avenue of exploration is the combination of camptothecins with angiostatin, endostatin, or vasculostatin, compounds that belong to the emerging class of endogenous inhibitors of angiogenesis (27, 30)." (p. 186, Col. 1, lines 21 to 24). The compounds defined by O'Leary *et al.* are members of a class of inhibitors that consists of small (20-40 kDa) protein molecules, which are generated by proteolytic degradation from large endogenous proteins. For example, endostatin is a 20 kDa proteolytic fragment of type XVIII collagen, angiostatin is a 38 kDa proteolytic fragment of plasminogen, and vasculostatin is a 20 kDa proteolytic fragment of nidogen-1. (*See* Folkman, J. *In:* E. M. Greenspan (ed.), Chemotherapy Foundation Symposium XV. Innovative Cancer

Therapy for Tomorrow, pp. 14-15. New York: The Chemotherapy Foundation, 1997; O'Reilly, *et al.* Cell, *88:* 277-285, 1997; PCT/US01/40382; attached hereto as Appendix B).

Sheibani *et al.* and Streit *et al.* describe thrombospondin-1 and thrombospondin-2. These molecules are members of a class of large (~180 kDa) extracellular matrix glycoproteins. Thus, the classes of angiogenesis inhibitors described by O'Leary *et al.* and Sheibani *et al.* or Streit *et al.* are fundamentally different.

The MPEP provides guidance regarding the obviousness of substituting one compound for another.

> A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). (*See* MPEP §2144.09).

Because of the significant differences in the size and structure of the compounds described by O'Leary *et al.* and those described by Sheibani *et al.* and Streit *et al.*, , one skilled in the art would have no expectation that these two classes of compounds would possess similar properties. Therefore, one skilled in the art would have no motivation to substitute the thrombospondins of the present invention for the small inhibitors suggested by O'Leary *et al.* Moreover, there is no suggestion in any of the cited references to combine them. In the absence of such a suggestion, a prima facie case of obviousness has not been established.

Even if O'Leary *et al.* is properly combined with Sheibani *et al.* and Streit *et al.*, Applicants submit that the facts of the present case overcome a *prima facie* determination of

obviousness. The invention was based on surprising results and a synergistic effect from the claimed combination of drugs. First, *in vitro* results indicated that combining a thrombospondin and an inhibitor of DNA topoisomerase did not produce enhanced cytotoxicity (page 6, lines 1-4, of the specification). In view of this result, one of skill in the art of cancer research would have stopped right there; an average researcher would not have been motivated to administer the combination of compounds to a mammal as claimed. Second, not only did the *in vivo* data indicate that the combined drug therapy of animals led to increased inhibition of tumor growth, a synergistic antineoplastic effect was observed after administration of TSP and CPT-11. (Specification at page 6, lines 4-5 of the specification).

Demonstration of surprising results and synergy are evidence of nonobviousness. Applicants submit that the data disclosed in the specification represent strong evidence that the invention as presently claimed is nonobvious over O'Leary *et al.* in view of Sheibani *et al.* and Streit *et al.* Therefore, withdrawal of this rejection is respectfully requested.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

A petition for extension of time and a check in the amount of $200.00 is enclosed to cover the petition fee for a two month extension of time pursuant to 37 C.F.R. § 1.17(a)(2). The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-038.

Respectfully submitted,

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Appendix A: Version with markings to show changes made

9. (Amended) A method of inhibiting tumor cell growth in a mammal, comprising administering to said mammal a composition comprising [an inhibitor of angiogenesis] a thrombospondin compound and an inhibitor of DNA topoisomerase I enzyme activity.

12. (Amended) The method of claim [10] 9, wherein said thrombospondin compound is thrombospondin-1.

13. (Amended) The method of claim [10] 9, wherein said thrombospondin compound is thrombospondin-2.

18. (Amended) The method of claim 9, wherein said [inhibitor of angiogenesis] thrombospondin compound is administered prior to said inhibitor of DNA topoisomerase I enzyme activity.

19. (Amended) The method of claim 9, wherein said inhibitor of DNA topoisomerase I enzyme activity is administered prior to said [inhibitor of angiogenesis] thrombospondin compound.

20. (Amended) The method of claim 9, wherein said [inhibitor of angiogenesis] thrombospondin compound and said inhibitor of DNA topoisomerase I enzyme activity are administered simultaneously.